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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,909	12/18/2001	Heather L. Davis	C1039/7058(HCL X04/19/02)	8458

7590 04/10/2007

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/023,909	DAVIS ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-13,20-33 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 8-13, 20-33, and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communications filed 10 April, 2006, 28 August, 2006, and 22 December, 2006. Claims 1, 8-13, 20-33, and 35 are pending and currently under examination.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

The previous rejection of claims 1, 8-13, 20-33, and 35 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is hereby withdrawn in response to applicants' amendment.

Enablement

Claims 1, 8-13, 20-33, and 35 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As previously set forth, the claims are broadly

directed toward methods for the induction of antigen-specific immune responses in a subject through the administration of antigen and a combination of adjuvants comprising a CpG dinucleotide and another non-nucleic acid adjuvant (e.g., MPL). The claims further stipulate that the CpG dinucleotide-containing oligonucleotide may vary in length between 8-100 nucleotides and contain at least one phosphate backbone modification.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide sufficient guidance pertaining to the structural requirements of any given ISS-ODN. The skilled artisan would require a knowledge of those sequences that should be included in any given ISS prior to practicing the invention. However, the disclosure fails to provide sufficient guidance pertaining to the composition and length of those sequences that produce a synergistic immune response when combined with another adjuvant. The claimed CpG-containing compounds may vary in length between 8 and 100 nucleotides and contain any one of a number of phosphate backbone modifications. The state-of-the-art (see item three below) clearly demonstrates that flanking sequences, as well as, backbone modifications can effect the adjuvant activities of

any given CpG-containing oligonucleotide in an unpredictable manner. Applicants' response fails to provide a sufficient amount of data addressing these concerns. Applicants' response fails to provide detailed structural guidance pertaining to the structural requirements for any given ISS.

2) The disclosure fails to provide adequate guidance pertaining to those immune stimulating adjuvants (e.g., saponins, MPL, MDP, etc.) that can reasonably be expected to produce a synergistic immune response when combined with another adjuvant. Vaccine development is an empirical process that requires extensive experimentation to identify suitable combinations of immunogen and adjuvant(s), routes of inoculation, and immunization regimens. Moreover, the claims require a synergistic effect from combining the CpG-containing ISS and other non-nucleic acid adjuvant. While the declaration of Dr. Hunter provides some evidence for a synergistic immune response (e.g., CpG-1826, alum, and HBSag), it also demonstrates that many combinations of ISS, adjuvant, and immunogen were not synergistic. Thus, the skilled artisan would still needs to know which combination of CpG-ODN, non-nucleic acid adjuvant, and immunogen should be employed.

3) The prior art is unpredictable and teaches that many putative ISS elements do not function in the manner desired and often fail to facilitate immune responses to the immunogen of interest. Contrary to applicants' assertion, flanking nucleotide sequences and phosphate backbone modifications can have unprdictable effects on the adjuvant activity of any give CpG-ODN (Hsieh *et al.*, 2004; Vollmer *et al.*, 2002; Pisetsky, 1999; Weiner, 2000; Manish *et al.*, 2004). Both Hsieh and colleagues and Manish and associates noted that while a specific CpG-ODNM increased generic immune responses against the immunogen of interest, this response was transient and did not lead to a neutralizing immune response. Weiner notes that flanking nucleotide sequences have unpredictable effects on the

immune activities of CpG-ODNs. Pisetsky suggested that caution must be employed when modifying the CpG-ODN phosphate backbone. Vollmer and colleagues concluded (see abstract, p. 165) that "the effect of both nucleotide content and PS backbone to stimulate human leukocytes is not well understood." The authors further reported that "ODNs rich in other nucleotides (guanosine, cytosine, or adenosine) induced no or much lower levels of immunostimulation. The observed effects were highly dependent on the PS backbone chemistry." Clearly, the skilled artisan cannot reasonably predict which combination of adjuvants will have a synergistic effect when employed concomitantly. In addition to those parameters governing CpG-ODNs, the effectiveness of any given preparation will also depend upon several factors including the antigen, adjuvants, dose, immunization regimen, and site of immunization. Because of the empirical nature of this process, the skilled artisan cannot reasonably predict which combinations of adjuvants will display synergistic effects when administered concomitantly with an immunogen. This is not surprising considering the complexity of the immune system. As set forth *supra*, the declaration of Dr. Hunter delt primarily with a single ISS, CpG-1826. Thus, it failed to directly address this point.

4) The claims are of considerable breadth and are not fully supported by the disclosure. The broadest claims are not limited to any particular CpG-ODN or immune stimulating adjuvant or immunogen. Accordingly, the claims literally encompass tens-of-thousands of permutations. However, the disclosure, declaration, and applicants' arguments fail to teach which combination(s) of immunogen, CpG-ODN, and adjuvant will produce the desired response.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

01 April, 2007